Master's Thesis

Supplementary Motor Area Epilepsy

– From Semiology to Electrophysiology –

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Abstract

Introduction: The objective of supplementary motor area (SMA) epilepsy surgery is complete resection or disconnection of epileptogenic zone while sustaining the functionally relevant eloquent cortex. Various diagnostic modalities are used to define the seizure onset zone and eloquent cortex. However, SMA epilepsy remains diagnostic challenge due to its location is concealed in mesial frontal lobe. The clinical characteristics of SMA epilepsy has been described as an abrupt tonic posturing one or more extremities, vocalization, without loss of consciousness. Nonetheless, due to preservation of consciousness, SMA epilepsy can be mistakenly diagnosed. Moreover, electrophysiological findings are also often misleading because of interictal spikes found in the midline have normal background rhythm and paradoxical lateralization. On the other hand, MEG as the latest neurophysiological tools, has great spatial resolution and high signal-to-noise ratio which offers several advantages over EEG in detecting epileptogenic foci in SMA epilepsy. Therefore in this study, we reevaluate presurgical diagnostic modalities and sought to find clinical value of MEG to localize epileptogenic zone in SMA epilepsy. Moreover, lateralizing value of semiology observed in patient group will also be determined.

Methods: Forty-four patients who underwent epilepsy respective surgery and had SMA removed were reviewed retrospectively. Clinical characteristics of each patients were assessed and its lateralizing value were calculated. Concordance of interictal VEM, PET, ictal SPECT, and MRI results to resection area were evaluated and related them to surgical outcome. Interictal spikes source

distribution in simultaneous EEG/MEG were done by using sLORETA separately to compare EEG and MEG sensitivity.

Results: The most reliable predictors of seizure lateralization were versive head movement and unilateral tonic posturing ($p=0.004$ and $p=0.021$, respectively), indicating contralateral lateralization in more than 90% of patients. Only interictal MEG significantly localized correctly in 7 of 9 patients with favorable outcome ($p=0.021$) and none of the non-favorable outcome patients showed abnormalities localized in epileptogenic lobe. In simultaneous EEG/MEG, 4 of 7 favorable outcome patients showed non-lateralizing interictal EEG, while 6 of 7 favorable outcome patients showed localized interictal MEG within resection area. One patient had MRI revealed tumor lesion in right SMA and also left hippocampal sclerosis, exclusively had interictal EEG spikes that constantly located in temporal lobe while interictal MEG spikes predominantly localized within resection area.

Conclusion: MEG is a useful tool in localizing epileptogenic zone, especially when EEG fails to localize or lateralize epileptogenic lesion in the midline area, such in SMA epilepsy case.

Keyword: Supplementary motor area (SMA), Epilepsy, Electroencephalography (EEG), Magnetoencephalography (MEG), Semiology, Electrophysiology

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Chapter 1. Introduction

1.1. Epilepsy

1.1.1. Definition

Epilepsy is a neurological condition characterized by recurrence of at least two unprovoked epileptic seizure which is transient signs and symptoms of abnormal, excessive excitation and synchronous neuronal activity in the brain (Fisher et al., 2014; Fisher et al., 2005).

1.1.2. Epidemiology

About 0.5−1% of general population suffer from epilepsy in which 80% of epilepsy patients in developing countries are not receiving inappropriate treatment (Atlas, 2005; Organization, 2009; Scott, Lhatoo, & Sander, 2001). Epilepsy causes disease burden not only because of early death but also because of long life disability and illness. The burden of epilepsy accounts for around 0.5% of the burden of all the diseases in the world, and contributes even more significantly to the burden caused by disability (Leonardi & Ustun, 2002). In addition to the measurable burdens, epileptic patients suffer more social and economic impacts.

1.2. SMA Epilepsy: Diagnostic Workup

Supplementary motor area (SMA) epilepsy is a type of frontal lobe epilepsy arising from supplementary motor area which has reciprocal connections to motor area, limbic area and sensory area (Morris,

Dinner, Luders, Wyllie, & Kramer, 1988; Vergani et al., 2014; Wiesendanger, 1981). The diagnosis of SMA epilepsy is based on combination of clinical history, physical examination and also assessment by using diagnostic tools. Seizure semiology is regarded as pivotal as other pre-surgical evaluation in localizing the seizure and should be describe as accurate as possible (Adams, Victor, Ropper, & Daroff, 1997). Beside ictal symptoms, information about the circumstances, timing, triggering factors and position must all be obtained.

The clinical characteristics of SMA epilepsy has been described as an abrupt tonic posturing one or more extremities, vocalization, without loss of consciousness, last for less than 1 minute and frequently occur during sleep (Morris et al., 1988). Moreover, tonic posturing in SMA epilepsy followed by clonic movements of all extremities can be mistakenly diagnosed as psychogenic non-epileptic epilepsy due to preservation of consciousness (Bass et al., 1995; Kanner et al., 1990). Therefore, diagnosing SMA epilepsy from semiology alone can mislead to different type of epilepsy.

Electrophysiological findings can help diagnosing SMA epilepsy when the epileptogenic focus is found at or near the vertex (C. Baumgartner et al., 1996; Morris et al., 1988). Previous report disclosed that half of patients with SMA epilepsy had IED foci in the midline (Fz or Cz) or in a frontocentral distribution (F3 or F4) (Blume & Oliver, 1996). However, these findings are often confused with normal EEG patterns during sleep due to interictal sharp waves in SMA epilepsy have normal background rhythms (Morris et al., 1988). Moreover, determining the epileptogenic focus can be difficult as the

location of SMA is concealed in the mesial frontal lobe especially when we use scalp EEG and the propagation of epileptogenic activity from SMA to adjacent area is also rapid and widespread (Holtkamp, Sharan, & Sperling, 2012; Laskowitz, Sperling, French, & O'Connor, 1995; Sato, Fukuda, Oishi, Shirasawa, & Fujii, 2013).

MEG is a useful noninvasive tool with great spatial resolution which offers several advantages over EEG in detecting epileptogenic foci. Compared to electric potentials, magnetic fields used in MEG are less distorted by conductivity of tissue layers between the brain and recording sensors (Hamalainen & Sarvas, 1989; Shiraishi et al., 2001). Moreover, MEG may reveal clear spikes that can be differentiated from ongoing background due to its less sensitivity to deep sources activity (de Jongh, de Munck, Gonçalves, & Ossenblok, 2005; Ossenblok, De Munck, Colon, Drolsbach, & Boon, 2007). Although there has been no reports that exclusively study about MEG in SMA epilepsy, but it has been indicated that interictal MEG gives useful localizing information in pre-surgical assessment of mesial frontal lobe epilepsy (Ossenblok et al., 2007; Shiraishi et al., 2001).

1.3. Objectives

The objective of supplementary motor area (SMA) epilepsy surgery is complete resection or disconnection of epileptogenic zone while sustaining the functionally relevant eloquent cortex. Various diagnostic modalities are used to define the seizure onset zone and eloquent cortex. A precise delineation of the epileptogenic zone takes part in achieving a good surgical outcome. However, localizing epileptogenic focus in SMA epilepsy is still technically challenging

due to interictal or ictal findings in non-invasive tools are often absent, non-lateralizing or misleading over paradoxical lateralization and usually required invasive monitoring which carries additional risk and expenses (Blume & Oliver, 1996; Hamer et al., 2002; Önal et al., 2003; Quesney, Constain, Fish, & Rasmussen, 1990). There are still limited study about SMA epilepsy particularly diagnostic approach using MEG. Thus, the main aim of this study was to assess the value of interictal EEG and MEG toward epileptogenic foci localization and lateralization in SMA epilepsy. In addition, localization from each modality was compared with surgical outcome to see the prognostic value. Moreover, semiology were identified to determine its lateralizing value to the resection area, expecting a helpful information in localizing epileptogenic zone.

Chapter 2. Methods

2.1. Patients

From a prospectively compiled database, we retrospectively studied consecutively epilepsy surgery cases performed at Seoul National University Hospital during a 17-year period from January 1994 to December 2011. Surgical candidates with drug-resistant epilepsy who underwent resective surgery in SMA structures were included. The diagnostic criteria used for SMA epilepsy were the presence of either a discrete lesion in SMA with a compatible ictal EEG, or the presence of an exclusive ictal onset zone in the SMA confirmed by intracranial EEG.

There were 25 male and 19 female patients ranging from 15 to 63 years (mean 35.3 ± 11.1 years) and the duration of illness from 0.1 to 30 years (mean 10.7 ± 8.3 years). Most patients experienced frequent seizures, with an average seizure frequency of 14 seizures per month (range 0.1 to 150 seizures per month).

2.2. Presurgical Evaluation

Preoperative evaluation to localize an ictal onset zone included a routine history, neurological examination, interictal video-EEG monitoring (VEM), ictal VEM, brain MRI, PET and interictal and ictal SPECT. If no definite lesion was identified via preoperative MRI, subdural electrodes would be implanted near the presumed near the presumed ictal onset zone according to VEM result while patients were under general anesthesia.

2.2.1. MR imaging

All patients underwent MR imaging either using a GE 1.0 or a 1.5T unit (Signa Advantage; General Electric Medical Systems, Milwaukee, WI) or a Siemens 1.5T scanner (MAGNETOM Avanto; Siemens, Erlangen, Germany). The section thickness and the conventional image gaps were 5 mm and 1 mm. T1-weighted 3D magnetization-prepares rapid acquisition of gradient-echo sequences with 1.5 mm thick sections of the whole brain and T2-weighted fluid-attenuated inversion recovery (FLAIR) images of 3 mm thick sections were also obtained in the oblique coronal plane of the temporal lobe. The angle of oblique imaging was perpendicular to long axis of the hippocampus. Spatial resolution was approximately 1.0 mm x 1.0 mm (matrix, 256 mm x 256 mm; field of view, 25 cm). MRI images were evaluated and the lobe containing abnormalities were then taken for further concordance analysis.

2.2.2. MEG-EEG Acquisition

Cortical magnetic activity recorded using a 306 channel, whole-head MEG system (VectorView^{TM}, Elekta Neuromag Oy, Helsinki, Finland) arranged in triplets of two planar gradiometers and one magnetometer in 13 patients and 60 or 128 channels of EEG were simultaneously recorded in 10 patients. Spontaneous MEG/EEG signals were obtained in a magnetically shielded room about 60 min while patients were supine and with eyes closed. The sampling rate was 600Hz with bandpass filter 0.1-200 Hz. In order to monitor eye movement and cardiac artifacts, a bipolar electro-oculogram and electrocardiogram were simultaneously recorded. Three anatomical fiducial points (nasion and bilateral preauricular points) and four

head-position indicator coils attached to the subject's head before the recording. The coil locations with respect to the anatomical reference points were measured using 3-D digitizer (FASTRAK^{TM}, Polhemus, Colchester, Vermont, USA). The temporal signal space separation (tSSS) was applied to eliminate the external interference signal that increase the SNR of the MEG signals (Taulu & Hari, 2009).

2.2.3. VEM Acquisition

In 25 patients, interictal/ictal scalp EEGs were recorded by using a VEM system with the electrodes placed according to the international 10-20 system, including anterior temporal electrodes. VEM was performed under the withdrawal of antiepileptic drugs except phenobarbital. Any interictal abnormalities were noted and used for analysis.

2.2.4. PET

PET was performed in 35 patients during interictal period. Axial raw data were pbtained on a PET scanner (ECAT EXACT 47, Siemens-CTI, Knokville, TN, USA) 60 min after the intravenous injection of ^{18}F-fluorodeoxyglucose (FDG; 370 MBq). The acquisition time was around 20 min. The axial images were then reconstructed by using a Shepp-Logan filter (cutoff frequency, 5 cycles per pixel) and realigned in the coronal and sagittal planes. Spatial resolution was 6.1 mm x 6.1 mm x 4.3 mm. PET images were evaluated and the lobe containing abnormalities were then taken for further concordance analysis.

2.2.5. Ictal SPECT

Ictal SPECT was performed in 18 patients during VEM. ^{99}Tc was

mixed with hecamethylpropylene amine oxime (HMPAO; 925 MBq) and injected as soon as a seizure started. Brain SPECT images were acquired within 2 hours of the injection using triple-head rotating Gamma camera (Prism 3000, Picker, USA) with high-resolution fan beam collimator. Using the step and shoot method at 3° intervals using a 128x128 matrix, brain perfusion SPECT was acquired. SPECT images were evaluated and the lobe containing abnormalities were then taken for further concordance analysis.

2.2.6. Clinical characteristic

The prior seizure history was taken from a witness or the patients themselves. Seizure semiology was then reviewed from the seizure history or VEM and classified according (Lüders et al., 1998).

2.4. MEG – EEG Data Analyses

The individual scalp and cortical surfaces of the patient were segmented from MRI volume data using Freesurfer image analysis suite (Fischl, 2012). A three-layer head model (Symmetric Boundary Element Method, BEM) was determined for each subject by using the software OpenMEEG embedded in Matlab based software Brainstorm for the forward model (Gramfort, Papadopoulo, Olivi, & Clerc, 2010; Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011).

Interictal epileptiform discharges in EEG recording were visually identified based on criteria defined by the International Federation of Clinical Neurophysiology (IFCN)(Deuschl & Eisen, 1999). MEG spikes were chosen for analysis based on duration (<80 msec), morphology, field map and lack of associated artifact. By using

Brainstorm, all visually detected interictal spikes from entire recording except in two patients who had ictal during recording were marked and used for source localization. Standardized low-resolution brain electromagnetic tomography (sLORETA) with the Brainstorm software was adopted as inverse algorithm (Pascual-Marqui, 2002). Since sLORETA returns as a current distribution, the point showing maximum F-distribution value was selected and assumed as the position best fitting to the real source location (Wagner, Fuchs, & Kastner, 2004).

2.5. Postsurgical Seizure Outcome and Pathology

The postoperative follow up duration was more than 2 years in all patients. Surgical outcome was analyzed using the Engel classification as 'favorable' (Engel class I and II) and 'unfavorable' (Engel class III and IV) categorization. Pathology was reviewed in all patients and was interpreted by neuropathologist.

2.6. Statistical Analyses

In semiology analysis, we performed nonparametric statistical analysis using the Sign test to evaluate the significance of frequency laterality with which the various motor signs occurred. The concordance analysis of MRI, interictal VEM, ictal VEM, PET, ictal SPECT and MEG interictal spike source localization with resection area were also evaluated and relate them to the surgical outcome. Interictal spike localization from EEG and MEG in 10 patients who underwent simultaneous EEG and MEG were compared and diagnostic sensitivities of each modality were calculated. The

localization was classified into four levels: localizing, lateralizing, non-lateralizing and false localizing in reference to resection area (Figure 1). The result was considered as localizing if the spikes were predominantly localized in epileptogenic lobe. As for lateralizing, the spike locations showed predominantly in the extended lobe of epileptogenic hemisphere and for non-lateralizing when there are no spike detected or spikes were located as multilobar pattern equally in both hemisphere. If the result came up predominantly on the other hemisphere either confined in one lobe or scattered, it will be classified as false localizing. Postoperative T1-weighted MRI was used to delineate the resection area. Chi-squared test was used for statistical significance in concordance analysis diagnostic modalities. All statistical analysis were performed by using SPSS 23.0 software (IBM, Armonk, New York, USA).

Chapter 3. Result

3.1. Patient Profiles

Profiles of the 44 SMA epilepsy patients are summarized in Table 1. Postoperative seizure outcome was Engel class I in 22 (50%) patients, class II in 9 (20.5%), class III in 6 (13.6%), and class IV in 7 (15.9%) patients. There were 25 (56.8%) male patients and 19 (43.2%) female patients. The mean age of the patients and seizure duration were 35.3±11.1 years (range 15-63 years) and 10.7±8.3 years (range 0.1-30.0 years), respectively. Tumor-like lesions were found in 18 patients (40.9%) and cortical lesions were found in 14 patients (31.8%) via preoperative MRI. Twelve patients (27.3%) showed no definite lesions on MRI.

3.2. Semiology

In our study, generalized tonic-clonic seizure (GTCS) was the most common clinical signs, present in more than half of the patients (Table 2). Of the motor signs, the most reliable predictors of seizure lateralization were versive head movement and unilateral tonic posturing (p=0.004 and p=0.021, respectively), indicating contralateral lateralization in more than 90% of patients.

3.3. Prognostic Value, Diagnostic Accuracy and Diagnostic of Various Non-invasive Presurgical Evaluations

3.3.1. Diagnostic Accuracy

We analyzed the prognostic value of the various modalities in 44 patients with at least a 2-year follow-up. VEM were performed in 25 patients. MRI was abnormal in 32 patients that correctly localized the lesion in 22 of 31 patients with favorable outcome and in 8 of 13 patients with non-favorable outcome, which was non-significant (p=392). Common findings were cerebromalacia and tumor. Ictal SPECT were performed in 18 patients, and correctly localized the lesion in 5 of 15 patients with favorable outcome and none of the non-favorable outcome patients had abnormality in epileptogenic lobe (p=0.350). FDG-PET correctly localized the lesion in 17 of 25 patients with favorable outcome, and in 5 of 10 non-favorable outcome patients. Interictal VEM showed correctly localizing spikes in 5 of 25 patients who achieved favorable outcome, and in 8 of 13 that did not (p=0.513). Interictal MEG localized correctly in 7 of 9 patients with favorable outcome (p=0.and none of the non-favorable outcome patients showed abnormalities localized in epileptogenic lobe. Detailed results from the diagnostic modalities were summarized in Table 3.

3.3.2. Prognostic Value

The positive predictive value of MRI, PET, ictal SPECT, interictal VEM, and interictal MEG, respectively were 70.9%, 68.0%, 33.3%, 29.4%, and 77.8%, and the negative predictive value were 38.5%, 50%, 100%, 37.5%, and 100%, respectively.

3.3. Simultaneous EEG-MEG

Ten patients underwent simultaneous EEG-MEG evaluations which 7 patients of those patients achieved favorable outcome after 2-year

of follow up. As shown in Table 4, patients with favorable outcomes tended to have MEG interictal spike localizing within the resection area, while the sources of MEG interictal spikes in 2 patients with unfavorable outcomes were lateralizing. The other non-favorable outcome patient had MEG interictal spikes dominantly located in parietal lobe contralateral to resection area. EEG interictal spikes sources in four of 7 patients with favorable outcome were non-lateralizing. The correlation between surgical outcome and interictal spike source localizing within resection area was significant in MEG ($p=0.033$). In patient 37, MEG interictal spikes localization was located within the resection area while EEG interictal spikes were constantly localized in left superior temporal gyrus (Figure 2).

Chapter 4. Discussion

SMA plays critical roles in voluntary motor control such as preparation, bimanual coordination, control of motor sequence, and selection of movements (Tanji, 1994). Thus, resection of SMA has resulted significant neurological deficits such as hemiparesis and aphasia that appear shortly after surgery. Although the deficits might resolve relatively well soon, but motor and speech function in complex task may be impaired (Kim et al., 2013; Zentner, Hufnagel, Pechstein, Wolf, & Schramm, 1996). Therefore, it is important to obtain the best seizure control and to conserve the SMA function.
In order to avoid functional deficits in SMA epilepsy patients undergo surgery, the present results give us clinically helpful information when considering the surgical indication and planning further presurgical evaluation.

4.1. Unilateral Tonic Posturing and Versive Head Movements lateralization in SMA Epilepsy

The clinical semiology of SMA epilepsy that has been widely accepted is characterized by sudden, brief tonic posturing of one or more extremities, vocalization, and also versive movement which may precede secondary generalization. These characteristics is supported by several studies that observed clinical symptoms in patients with SMA seizures as well as on cortical stimulation over SMA (Morris et al., 1988; Penfield, 1950; Penfield & Welch, 1951).
Our study showed that secondary generalized tonic clonic seizures (2GTCs) is the most prominent ictal symptoms among all the patients included in this study. Possible reason is due to rapid propagation of epileptic discharges to adjacent area of SMA (Unnwongse, Wehner,

& Foldvary-Schaefer, 2012).

Our result showed that unilateral tonic posturing is common in our subject groups. Furthermore, unilateral tonic posturing has high lateralizing value, as observed in contralateral to epileptogenic area found in 9 patients (Janszky, Fogarasi, Jokeit, & Ebner, 2001). Previous study that reported that unilateral tonic posturing is a distinct feature of SMA epilepsy compare to bilateral tonic posturing and was more frequently observed in SMA epilepsy rather than in extra-SMA epilepsy supports our findings (Sitthinamsuwan et al., 2016). Even though electrical stimulation of the SMA usually provoke bilateral and proximal tonic limb posturing, epileptic activation may develop in only unilateral tonic posturing in the contralateral limbs (Lim et al., 1994). Bilateral tonic posturing found in 2 patients may be caused by bilateral activation of SMA from seizure activity originating elsewhere due to strong interhemispheric connections between the two SMA with other cortical structures (C. Baumgartner et al., 1996; Ikeda, LÜDERS, Burgess, & Shibasaki, 1992; Wiesendanger, Rouiller, Kazennikov, & Perrig, 1996).

Another finding that significantly showed lateralizing value is versive head movements which are found in 20.5% of our subject group which is strongly associated with mesial frontal lobe seizure (Cotte-Rittaud & Courjon, 1962; Laich et al., 1997; Manford, Fish, & Shorvon, 1996). These significant findings of lateralizing value can help making decision to perform surgery or invasive recording.

4.2. MEG Provide More Useful Localizing Information in SMA Epilepsy Presurgical Evaluation

Determining epileptic focus in SMA epilepsy can be difficult, especially those with no identified anatomical lesion. Epileptic discharges from SMA can propagate rapidly and widespread, due to its connections to multiple reciprocal connections to primary

sensorimotor cortex, anterior cingulate cortex and various parietal somatosensory area (Hatanaka et al., 2003; Luppino, Matelli, Camarda, & Rizzolatti, 1993). Furthermore, its secluded location in the mesial frontal lobe complicates the investigation with scalp EEG, requiring invasive electrodes implanted chronically (Morris et al., 1988). However, because of the reason above, the location for invasive electrode location needs to be confirmed by various diagnostic workup to get precise seizure onset zone and reduce the risk of neurological deficits following surgery.

In the present study, our findings showed that MEG is the only modality that significantly related to favorable outcome in SMA epilepsy, especially compare to EEG. As the latest neurophysiological modality, MEG has several advantages over EEG in discovering epileptogenic foci. Not only MEG has superior signal-to-noise ratio than EEG, but also capable of determining epileptogenic focus located deeply fissure (Laskowitz et al., 1995; Ossenblok et al., 2007; Shiraishi et al., 2001).

In Shiraishi study, two of four patients with interictal EEG spikes occurred at CZ or Fz had interictal MEG spikes localized around the supplementary area. Even though they did not relate it to surgical outcome in their study, but they had claimed that MEG can be a helpful diagnostic modality for detecting epileptic focus when EEG spikes showed in midline region. Similar to our findings in simultaneous EEG/MEG, interictal EEG spikes localization in three patients with favorable outcome showed non-lateralizing while interictal MEG spikes localized within the resection area. Furthermore, interictal EEG spikes were constantly localized at left temporal lobe in patient 37 confirmed left hippocampal sclerosis found in MRI whereas interictal MEG spikes were distributed within the resection area, confirming epileptogenicity of tumor in SMA.

Poor localizing value of scalp electroencephalography can mislead the diagnosis of SMA epilepsy (Tükel & Jasper, 1952). Even though

electroencephalographic signals manifest in the midline, they can be easily missed by surface electrode, resulting in frequent secondary bilateral synchrony (Boesebeck, Schulz, May, & Ebner, 2002; Wieser & Hajek, 1995). Another possible reason of these findings is due to sensitivity of MEG to spikes arise from major fissures or gyral cortical planes that have an orientation that produce tangential fields such as temporal base, superior temporal plane, temporal tip, orbitofrontal cortex, inferior frontal opercular cortex occipital base and mesial sagittal fissure cortex. Therefore MEG measures predominantly activity in superficial neocortex, while EEG is more suited to detect deep sources (Christoph Baumgartner, Pataraia, Lindinger, & Deecke, 2000; Leijten, Huiskamp, Hilgersom, & van Huffelen, 2003).

4.3. Limitations

In this study we evaluated various diagnostic modalities and assessed clinical value of MEG to localize epileptogenic zone in SMA epilepsy. The significance of interictal MEG localization in SMA epilepsy was discussed for the first time in the literature. However, even this large analysis is not without limitations. Since this study obtained data retrospectively from 17 years of compiled database, epileptogenic zone localization of VEM, PET and SPECT were mainly collected from analog data. Therefore concordance between epileptogenic zone acquired from diagnostic modality and resection area retrieved from post-surgical MRI can only be based from the lobe containing the abnormality. Further analysis including more patients are necessary to determine more accurate clinical value of MEG in SMA epilepsy. Potentially, simultaneous EEG/MEG combined source analysis that has been reported improving source reconstruction are expected to be investigated in the future.

4.4. Conclusion

Versive head movement and unilateral tonic posturing were most reliable predictors of seizure lateralization, indicating contralateral lateralization in more than 90% of patients each group. Moreover, epileptogenic localization of MEG interictal discharges was significantly associated with long term post-surgical outcome. Lastly, MEG is a useful in localizing epileptogenic zone, especially when EEG fails to localize or lateralize epileptogenic lesion in the midline area, such in SMA epilepsy case.

Tables

Table 1. Patient profiles

#	Sex	Age	MRI Finding	Seizure frequency (month)	Surgery side	Resected area	Histology	Engel Class
1	M	36	Lt F closed lip type schizencephaly with heterotopia	2.0	Lt	Whole SMA	CD	1
2	M	34	Lt F medial & premotor tumor	4.0	Lt	Whole SMA	ODG	1
3	F	15	Rt F cortical atrophy	6.0	Rt	Whole SMA	CD	1
4	F	43	Rt F tumor	10.0	Rt	Whole SMA	ODG	1
5	M	24	WNL	5.0	Rt	Whole SMA	CD	2
6	M	26	WNL	60.0	Rt	Whole SMA	CD	1
7	M	23	WNL	20.0	Rt	Whole SMA	CD	4
8	M	28	WNL	0.5	Lt	Whole SMA	CD	3
9	M	23	Rt F large cystic cerebromalacia	10.0	Rt	Whole SMA	CD	2
10	M	45	Rt F tumor	3.0	Rt	Whole SMA	ODG	4
11	M	30	WNL	3.0	Rtt	Whole SMA	CD	3
12	M	40	Lt F tumor	0.1	Lt	Whole SMA	ODG	1
13	F	30	Rt SFG, non-specific lesion	150.0	Rt	Whole SMA	CD	1
14	M	16	Rt F medial, CD	30.0	Lt	Whole SMA	CD	2
15	M	30	WNL	60.0	Lt	Whole SMA	CD	1
16	M	52	Rt F tumor	1.0	Rt	Whole SMA	ODG	2
17	M	20	WNL	30.0	Rt	Pre-SMA	CS	2
18	M	31	Lt F, cerebromalacia	4.0	Lt	Pre-SMA	CS	1
19	F	28	WNL	2.0	Lt	Pre-SMA	CD	3
20	F	22	Lt F, AVM, cerebromalacia	8.0	Lt	Pre-SMA	AVM	1
21	F	17	WNL	6.0	Rt	Pre-SMA	CD	2
22	F	28	Ant F atrophy, corpus callosum agenesis	10.0	Lt	Pre-SMA	CM	4

23	M	19	Rt MFG, focal thickening	6.0	Rt	Pre-SMA	CD	1
24	F	37	WNL	2.0	Lt	Pre-SMA	CD	1
25	F	51	Lt SFG, MFG, cortical thickening	90.0	Lt	Pre-SMA	CD	1
26	M	41	Lt F, tumor	0.3	Lt	Pre-SMA	AA	1
27	F	19	Lt F, schizencephaly	0.5	Lt	SMA Proper	CH	2
28	F	57	Rt F, tumor	0.1	Rt	SMA Proper	CA	1
29	F	31	WNL	6.0	Lt	SMA Proper	CD	2
30	M	39	Lt superior F, tumor	0.1	Lt	SMA Proper	AO	1
31	M	25	WNL	15.0	Rt	SMA Proper	CD	4
32	F	27	Lt F, cerebromalacia	60.0	Lt	SMA Proper	CC	3
33	F	43	Lt sup F, tumor	0.4	Lt	SMA Proper	Ast	4
34	M	24	Lt sup F, tumor	1.0	Lt	SMA Proper	GGO	1
35	F	23	Rt FT, cerebromalacia	2.0	Rt	SMA Proper	CI	1
36	F	33	Lt F, tumor	2.0	Lt	SMA Proper	GBL	3
37	M	24	Rt F tumor, Lt HS	5.0	Rt	SMA Proper	ODG	1
38	M	40	Lt F, tumor	0.1	Lt	SMA Proper	ODG	2
39	F	32	Lt F, tumor	0.5	Lt	SMA Proper	ODG	1
40	M	19	Lt F, tumor	0.5	Lt	SMA Proper	RG	4
41	M	38	Rt F, tumor	5.0	Rt	SMA Proper	AA	3
42	M	63	Lt F, tumor	6.0	Lt	SMA Proper	AO	4
43	F	37	Rt F, tumor	1.0	Rt	SMA Proper	EVN	1
44	F	38	Lt F, cerebromalacia	2.0	Lt	Whole SMA	CD	1

Abbreviation: *AA,* Anaplastic Astrocytoma; *AO,* Anaplastic Oligodendroglioma; *AVM,* Arteriovenous Malformation; *CA,* Cavernous Angioma; *CC,* Cortical Contusion; *CD,* Cortical Dysplasia; *CH,* Cortical Heteropia; *CI,* Cortical Ischemia; *CM,* Cerebromalacia; *CS,* Cortical Scar; *EVN,* Extraventricular Neurocytoma; *GBL,* Glioblastoma; *GGO,* Ganglioglioma; *F,* Frontal; *FT,* Frontotemporal; *HS,* Hippocampal Sclerosis; *Lt,* Left; *MFG,* Medial Frontal Gyrus; *ODG,* Oligodendroglioma; *RG,* Reactive Gliosis; *Rt,* Right; *SFG,* Superior Frontal Gyrus; *sup,* superior; *WNL,* Within Normal Limit

Table 2. Semiology

Feature	Frequency	Predictive value (lateralization relative to seizure focus)
Versive head movement	9 (20.5%)	100% contralateral (p=0.004)
Bilateral tonic posturing	2 (4.5%)	–
Secondary generalized tonic–clonic seizure	25 (56.8%)	–
Unilateral dystonic posturing	8 (18.2%)	75% Contralateral (p=0.289)
Unilateral tonic posturing	10 (22.7%)	90% Contralateral (p=0.021)
Unilateral automatisms	7 (15.9%)	71.4% Ipsilateral (p=0.453)
Unilateral clonic movement	4 (9%)	100% Contralateral (p=0.125)
Oroalimentary automatism	5 (12%)	80% Contralateral (p=0.375)
Hypermotor	4 (9.1%)	–
Loss of consciousness	6 (13.6%)	–
Vocalization	5 (11.4%)	–

Table 3. The relationship between concordant lesion or epileptiform abnormalities on each diagnostic modalities and surgical outcome

a. MRI (p = 0.392)

	Favorable outcome	Unfavorable outcome	Total
Concordant	22	8	30
Non-concordant	9	5	14
Total	31	13	44

b. PET (p = 0.269)

	Favorable outcome	Unfavorable outcome	Total
Concordant	17	5	22
Non-concordant	8	5	13
Total	25	10	35

c. Ictal SPECT (p = 0.350)

	Favorable outcome	Unfavorable outcome	Total
Concordant	5	0	5
Non-concordant	10	3	13
Total	15	3	18

d. Interictal VEM (p = 0.513)

	Favorable outcome	Unfavorable outcome	Total
Concordant	5	3	8
Non-concordant	12	5	17
Total	17	8	25

e. Interictal MEG (p = 0.021)

	Favorable outcome	Unfavorable outcome	Total
Concordant	7	0	7
Non-concordant	2	4	6
Total	9	4	13

Table 4. Prognostic value of each diagnostic modalities

Presurgical Evaluation	PPV (%)	NPV (%)
MRI	70.9	38.5
PET	68.0	50
Ictal SPECT	33.3	100
Interictal VEM	29.4	37.5
Interictal MEG	77.8	100

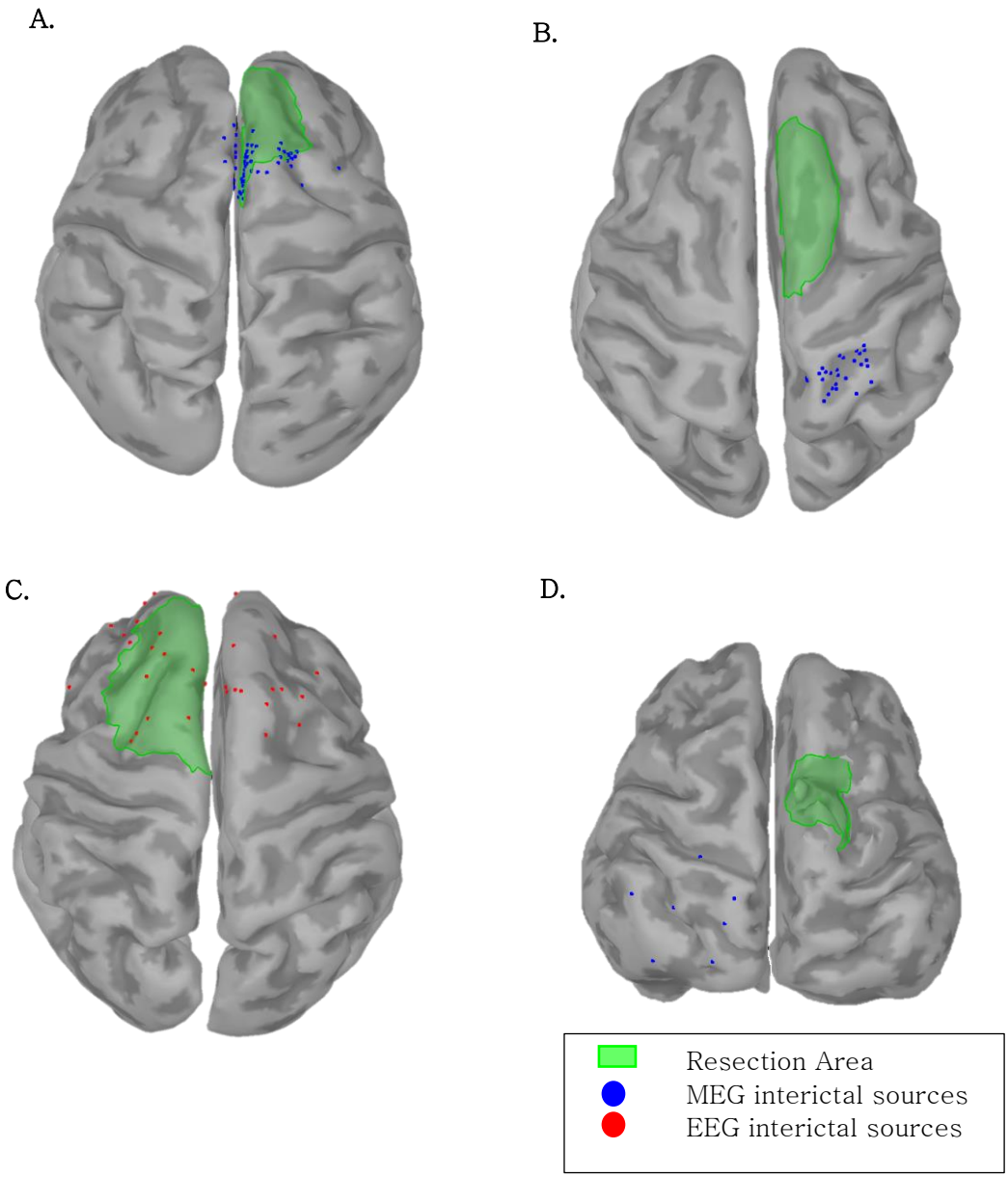
Table 5. Diagnostic Sensitivities of Simultaneous EEG-MEG

	Localizing	**Lateralizing**	**Non-lateralizing**	**False localizing**
EEG	**2/2**	**0/1**	**4/6**	**1/1**
MEG	**6/6**	**0/2**	**1/1**	**0/1**

*(favorable outcome/total)

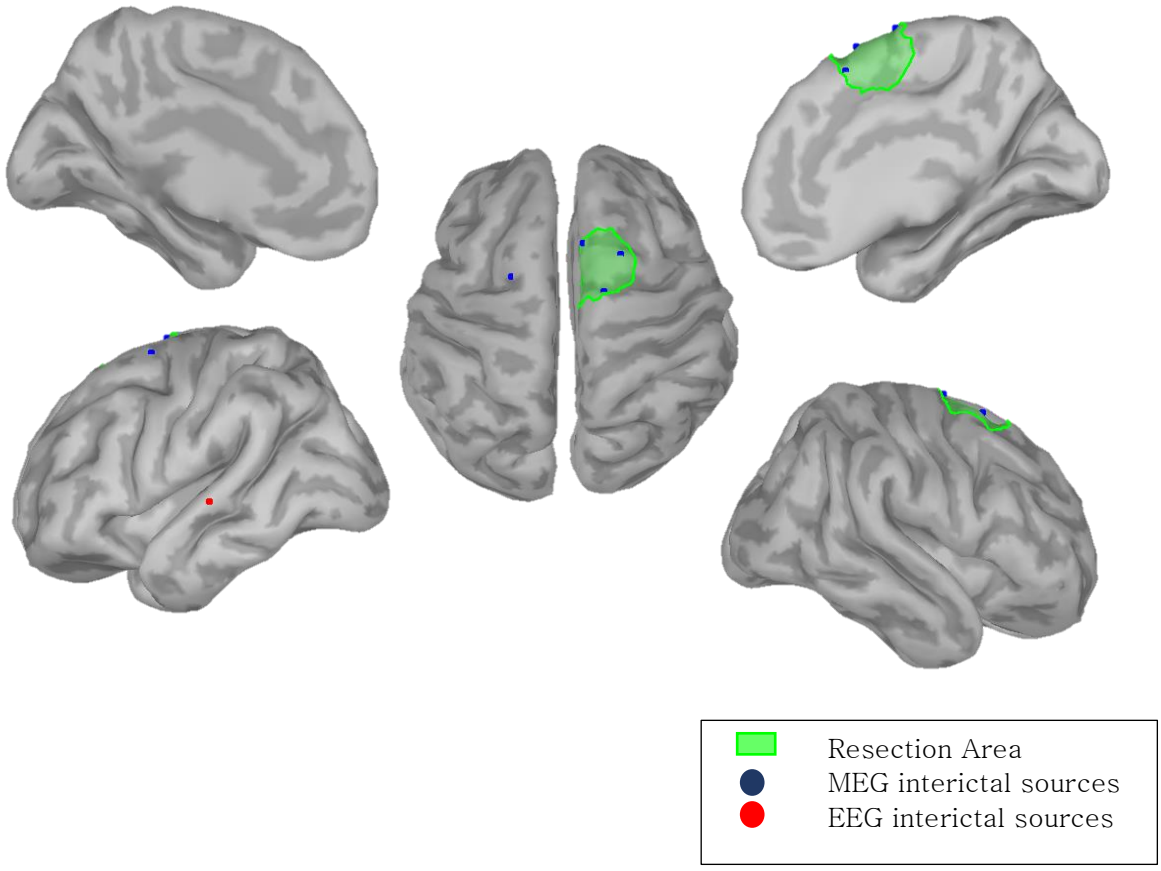
Figures

Figure 1. Classification of Interictal Spikes Localization



A. Localizing source distribution in patient 13
B. Lateralizing source distribution in patient 11
C. Non-lateralizing source distribution in patient 14
D. False localizing source distribution in patient 41

Figure 2. Simultaneous EEG/MEG in Patient 37



Interictal EEG spikes were constantly localized at left temporal lobe in patient 37 confirmed left hippocampal sclerosis found in MRI whereas interictal MEG spikes were predominantly distributed within the resection area, confirming epileptogenicity of tumor in right SMA

Bibliography

Adams, R. D., Victor, M., Ropper, A. H., & Daroff, R. B. (1997). Principles of neurology. *Cognitive and Behavioral Neurology, 10*(3), 220.

Atlas, W. (2005). Epilepsy care in the world. *Geneva: World Health Organization*, 8-16.

Bass, N., Wyllie, E., Comair, Y., Kotagal, P., Ruggieri, P., & Holthausen, H. (1995). Supplementary sensorimotor area seizures in children and adolescents. *J Pediatr, 126*(4), 537-544.

Baumgartner, C., Flint, R., Tuxhorn, I., Van Ness, P. C., Kosalko, J., Olbrich, A., . . . Luders, H. O. (1996). Supplementary motor area seizures: propagation pathways as studied with invasive recordings. *Neurology, 46*(2), 508-514.

Baumgartner, C., Pataraia, E., Lindinger, G., & Deecke, L. (2000). Neuromagnetic recordings in temporal lobe epilepsy. *Journal of Clinical Neurophysiology, 17*(2), 177-189.

Blume, W. T., & Oliver, L. M. (1996). Noninvasive electroencephalography in supplementary sensorimotor area epilepsy. *Adv Neurol, 70*, 309-317.

Boesebeck, F., Schulz, R., May, T., & Ebner, A. (2002). Lateralizing semiology predicts the seizure outcome after epilepsy surgery in the posterior cortex. *Brain, 125*(10), 2320-2331.

Chua, K., Chandran, V., Rajendra Acharya, U., & Lim, C. (2009). Analysis of epileptic EEG signals using higher order spectra. *Journal of medical engineering & technology, 33*(1), 42-50.

Cotte-Rittaud, M., & Courjon, J. (1962). Semiological value of adversive epilepsy. *Epilepsia, 3*(2), 151-166.

de Jongh, A., de Munck, J. C., Gonçalves, S. I., & Ossenblok, P. (2005). Differences in MEG/EEG epileptic spike yields explained by regional differences in signal-to-noise ratios. *Journal of clinical neurophysiology, 22*(2), 153-158.

Deuschl, G., & Eisen, A. (1999). Recommendations for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology.

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781.

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., . . . Glynn, M. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia, 55*(4), 475-482.

Fisher, R. S., Boas, W. v. E., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. (2005). Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia, 46*(4), 470-472.

Gramfort, A., Papadopoulo, T., Olivi, E., & Clerc, M. (2010). OpenMEEG: opensource software for quasistatic bioelectromagnetics. *Biomedical engineering online, 9*(1), 1.

Hamalainen, M. S., & Sarvas, J. (1989). Realistic conductivity geometry model

of the human head for interpretation of neuromagnetic data. *IEEE transactions on biomedical engineering, 36*(2), 165-171.

Hamer, H., Morris, H., Mascha, E., Karafa, M., Bingaman, W., Bej, M., . . . Hahn, J. (2002). Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology, 58*(1), 97-103.

Hatanaka, N., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., . . . Takada, M. (2003). Thalamocortical and intracortical connections of monkey cingulate motor areas. *Journal of Comparative Neurology, 462*(1), 121-138.

Holtkamp, M., Sharan, A., & Sperling, M. R. (2012). Intracranial EEG in predicting surgical outcome in frontal lobe epilepsy. *Epilepsia, 53*(10), 1739-1745.

Ikeda, A., LÜDERS, H. O., Burgess, R. C., & Shibasaki, H. (1992). Movement-related potentials recorded from supplementary motor area and primary motor area. *Brain, 115*(4), 1017-1043.

Janszky, J., Fogarasi, A., Jokeit, H., & Ebner, A. (2001). Lateralizing value of unilateral motor and somatosensory manifestations in frontal lobe seizures. *Epilepsy research, 43*(2), 125-133.

Kanner, A. M., Morris, H. H., Luders, H., Dinner, D. S., Wyllie, E., Medendorp, S. V., & Rowan, A. J. (1990). Supplementary motor seizures mimicking pseudoseizures: some clinical differences. *Neurology, 40*(9), 1404-1407.

Kim, Y. H., Kim, C. H., Kim, J. S., Lee, S. K., Han, J. H., Kim, C. Y., & Chung, C. K. (2013). Risk factor analysis of the development of new neurological deficits following supplementary motor area resection. *J Neurosurg, 119*(1), 7-14. doi:10.3171/2013.3.JNS121492

Lüders, H., Acharya, J., Baumgartner, C., Benbadis, S., Bleasel, A., Burgess, R., . . . Geller, E. (1998). Semiological seizure classification. *Epilepsia, 39*(9), 1006-1013.

Laich, E., Kuzniecky, R., Mountz, J., Liu, H. G., Gilliam, F., Bebin, M., . . . Morawetz, R. (1997). Supplementary sensorimotor area epilepsy. Seizure localization, cortical propagation and subcortical activation pathways using ictal SPECT. *Brain, 120 (Pt 5)*, 855-864.

Laskowitz, D. T., Sperling, M. R., French, J. A., & O'Connor, M. J. (1995). The syndrome of frontal lobe epilepsy Characteristics and surgical management. *Neurology, 45*(4), 780-787.

Leijten, F. S., Huiskamp, G.-J. M., Hilgersom, I., & van Huffelen, A. C. (2003). High-resolution source imaging in mesiotemporal lobe epilepsy: a comparison between MEG and simultaneous EEG. *Journal of Clinical Neurophysiology, 20*(4), 227-238.

Leonardi, M., & Ustun, T. B. (2002). The global burden of epilepsy. *Epilepsia, 43*(s6), 21-25.

Lim, S., Dinner, D., Pillay, P., Lüders, H., Morris, H., Klem, G., . . . Awad, I. (1994). Functional anatomy of the human supplementary sensorimotor area: results of extraoperative electrical stimulation. *Electroencephalography and clinical neurophysiology, 91*(3), 179-193.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical

connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparative Neurology, 338*(1), 114-140.
Manford, M., Fish, D., & Shorvon, S. (1996). An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. *Brain, 119*(1), 17-40.
Morris, H. H., 3rd, Dinner, D. S., Luders, H., Wyllie, E., & Kramer, R. (1988). Supplementary motor seizures: clinical and electroencephalographic findings. *Neurology, 38*(7), 1075-1082.
Önal, Ç., Otsubo, H., Araki, T., Chitoku, S., Ochi, A., Weiss, S., . . . Rutka, J. T. (2003). Complications of invasive subdural grid monitoring in children with epilepsy. *J Neurosurg, 98*(5), 1017-1026.
Organization, W. H. (2009). Fact sheet No. 999: Epilepsy. Retrieved April 2nd, 2009.
Ossenblok, P., De Munck, J. C., Colon, A., Drolsbach, W., & Boon, P. (2007). Magnetoencephalography is more successful for screening and localizing frontal lobe epilepsy than electroencephalography. *Epilepsia, 48*(11), 2139-2149.
Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol, 24*(Suppl D), 5-12.
Penfield, W. (1950). The supplementary motor area in the cerebral cortex of man. *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr, 185*(6-7), 670-674.
Penfield, W., & Welch, K. (1951). The supplementary motor area of the cerebral cortex; a clinical and experimental study. *AMA Arch Neurol Psychiatry, 66*(3), 289-317.
Quesney, L., Constain, M., Fish, D., & Rasmussen, T. (1990). The clinical differentiation of seizures arising in the parasagittal and anterolaterodorsal frontal convexities. *Archives of neurology, 47*(6), 677-679.
Sato, Y., Fukuda, M., Oishi, M., Shirasawa, A., & Fujii, Y. (2013). Ictal near-infrared spectroscopy and electrocorticography study of supplementary motor area seizures. *Journal of biomedical optics, 18*(7), 076022-076022.
Scott, R. A., Lhatoo, S. D., & Sander, J. W. (2001). The treatment of epilepsy in developing countries: where do we go from here? *Bulletin of the World Health Organization, 79*(4), 344-351.
Shiraishi, H., Watanabe, Y., Watanabe, M., Inoue, Y., Fujiwara, T., & Yagi, K. (2001). Interictal and ictal magnetoencephalographic study in patients with medial frontal lobe epilepsy. *Epilepsia, 42*(7), 875-882.
Sitthinamsuwan, B., Usui, N., Tottori, T., Terada, K., Kondo, A., Matsuda, K., . . . Inoue, Y. (2016). Seizures with tonic posturing: Semiologic difference between supplementary sensorimotor area (SSMA) origin and extra-SSMA origin. *Epilepsia, 57*(2), e39-e44.
Tükel, K., & Jasper, H. (1952). The electroencephalogram in parasagittal lesions. *Electroencephalography and clinical neurophysiology, 4*(4), 481-494.

Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: a user-friendly application for MEG/EEG analysis. *Computational intelligence and neuroscience, 2011*, 8.

Tanji, J. (1994). The supplementary motor area in the cerebral cortex. *Neurosci Res, 19*(3), 251-268.

Taulu, S., & Hari, R. (2009). Removal of magnetoencephalographic artifacts with temporal signal-space separation: demonstration with single-trial auditory-evoked responses. *Human brain mapping, 30*(5), 1524-1534.

Unnwongse, K., Wehner, T., & Foldvary-Schaefer, N. (2012). Mesial frontal lobe epilepsy. *Journal of Clinical Neurophysiology, 29*(5), 371-378.

Vergani, F., Lacerda, L., Martino, J., Attems, J., Morris, C., Mitchell, P., . . . Dell'Acqua, F. (2014). White matter connections of the supplementary motor area in humans. *J Neurol Neurosurg Psychiatry, 85*(12), 1377-1385. doi:10.1136/jnnp-2013-307492

Wagner, M., Fuchs, M., & Kastner, J. (2004). Evaluation of sLORETA in the presence of noise and multiple sources. *Brain topography, 16*(4), 277-280.

Wiesendanger, M. (1981). Organization of secondary motor areas of cerebral cortex. *Comprehensive Physiology*.

Wiesendanger, M., Rouiller, E. M., Kazennikov, O., & Perrig, S. (1996). Is the supplementary motor area a bilaterally organized system? *Advances in neurology, 70*, 85-93.

Wieser, H., & Hajek, M. (1995). Frontal lobe epilepsy: compartmentalization, presurgical evaluation, and operative results. Discussion. *Advances in neurology, 66*, 297-319.

Zentner, J., Hufnagel, A., Pechstein, U., Wolf, H. K., & Schramm, J. (1996). Functional results after resective procedures involving the supplementary motor area. *Journal of neurosurgery, 85*(4), 542-549.

Abstract

서론 : 보조 운동 영역의 뇌전증 수술은 피질의 주요 기능을 보존하는 동시에 뇌전증 유발부위를 완전히 절제하거나, 정상 대뇌와의 단절을 이루는 것을 목표로 한다. 발작 시작 영역과 피질의 주요 기능 영역을 밝히기 위해 다양한 진단 방법들이 사용되고 있다. 하지만, 보조 운동 영역의 뇌전증 병변이 내측 전두엽에 위치해 있기 때문에 정확한 진단이 쉽지 않다.
보조 운동 영역 뇌전증의 임상적 특성은, 의식 상실을 동반하지 않는 사지와 발성의 갑작스러운 강직성 동작에 있다.
그러나 의식이 보존되어 있기 때문에, 보조 운동 영역 뇌전증은 잘못 진단할 수도 있다.
또한, 발작간극파를 보이는 정중선에서의 정상적인 리듬과 편향화 때문에 전기 생리학적 발견들은 종종 오해의 소지가 있다
반면에, 가장 최근의 신경 생리학적 도구인 MEG는 EEG와 비교하여 공간 분해능이 우수하고 신호 대 잡음비가 높기 때문에 보조 운동 영역 뇌전증 원인 병소 진단에 유용하다.
따라서, 이 연구에서는 술전 진단 양상을 재평가하고 보조 운동 영역 뇌전증의 발작 시작 위치를 알아내는 MEG의 임상 가치를 모색하였다.
또한, 환자에서 나타나는 임상증후의 편측화 가치를 결정 할 수 있었다.

방법:뇌전증 수술을 했고 SMA를 제거한 44명의 환자들을 확인하여 각 환자의 임상적 특성과 편측화 값을 산정했다.
MRI 결과에서 발견된 절제술 부분과 VEM 발작간기, PET, SPECT 발작성의 일치를 확인하고 수술 결과를 평가했다.
EEG 및 MEG 민감도를 각각 비교하기 위하여 simultaneous EEG/MEG의 발작간극파 는 sLORETA를 별도로 사용하였다.

결과: Versive head rotation 및 unilateral tonic posturing은 90% 이상

환자에서 contralateral lateralization이 나타나 좌우 기능 분화로 가장 신뢰할 만 하였다.
9명 중 7명의 favorable outcome 환자들에서 오직 interictal MEG가 상당히 정확하게 국소화되었고 non-favorable outcome 환자중 epileptogenic lob는 아무 이상이 없었다

결론: 보조 운동 영역 뇌전증에서 MEG는 발작 시작 영역 위치를 알아낼 때 유능한 진단 도구이다. 특히 EEG가 뇌전증 발작 시작 영역 위치나 좌우의 기능 분화를 하지 못한 경우와 비교하여 뛰어나다.